L3: Entry 1 of 3 File: DWPI Jun 17, 2004

DERWENT-ACC-NO: 2002-179800
DERWENT-WEEK: 200440

TITLE: Selecting compounds that inhibit herpes viruses by comparing inhibitory concentration of a compound of interest that inhibits wild-type herpes virus and domain mutant herpes virus, and selecting compound of interest

INVENTOR: HOMA, F L; HOPKINS, T A ; THOMSEN, D R ; WATHEN, M W .

PRIORITY-DATA: 2001US-283880P (April 13, 2001), 2000US-218118P (July 13, 2000), 2001US-0904065 (July 12, 2001), 2003US-0692556 (October 24, 2003)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 20040115623 A1	June 17, 2004		000	C12Q001/70
WO 200206513 A2	January 24, 2002	E	126	C12Q001/00
AU 200172920 A	January 30, 2002		000	C12Q001/00
US 20020076789 A1	June 20, 2002		000	A61K048/00
US 6682892 B2	January 27, 2004		000	C12Q001/68

INT-CL (IPC): A01 N 43/04; A61 K 31/70; A61 K 48/00; C07 H 21/04; C12 N 9/22; C12 Q 1/00; C12 Q 1/68; C12 Q 1/70

ABSTRACTED-PUB-NO: US20020076789A
BASIC-ABSTRACT:

NOVELTY - Selecting (M) compounds that inhibit herpes viruses involves measuring IC50 of compound of interest (CI) that inhibits wild-type herpes virus (I) and domain mutant herpes virus (II) which is the same strain as (I), comparing IC50 of CI inhibiting (I) with IC50 of CI inhibiting (II) and selecting CI, where IC50 of CI that inhibits (II) is at least 3 times greater than IC50 of CI that inhibits (I).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a compound (III) for inhibiting herpes virus DNA polymerases, where passage of a wild type herpes virus in the presence of the compound results in a change of wild type herpes simplex virus type 1 (HSV-1) polymerases at amino acid 823 from valine to alanine, or of human cytomegalovirus (HCMV) polymerases at amino acid 823 from valine to alanine and at amino acid 824 from valine to leucine;

(2) a mutant herpes virus DNA molecule (IV) having a nucleotide sequence comprising

3717, 3723, 3708, or 3729 base pairs fully defined in the specification; and

(3) a mutant herpes virus polymerase amino acid molecule (V) having a sequence comprising 1238, 1240, 1235, or 1242 amino acids fully defined in the specification.

ACTIVITY - Antiviral.

MECHANISM OF ACTION - Inhibitor of herpes virus (claimed).

Antiviral activity of nucleoside and non-nucleoside polymerase inhibitors against 4-oxo-dihydroquinoline (4-oxo-DHQ) resistant mutants was tested: In order to determine if the 4-hydroxyquinoline (4-HQ) binding domain mutations altered the sensitivity of the herpes simplex virus type-1 (HSV-1), HSV-2 and human cytomegalovirus (HCMV) mutants to both non-nucleoside (4-oxo-DHQ's) and nucleoside inhibitors (e.g., Acyclovir and ganciclovir) several of the mutants were tested in plaque reduction assays against a series of non-nucleoside compounds including Foscarnet (PFA), 4-HQ's 4-oxo-DHQ's and 4-oxo-dihydrothienopyridine (4-oxo-DHTP). The mutants were also tested against series of nucleoside inhibitors including Acyclovir and ganciclovir. The activity of these compounds against the mutant was compared to their activity against the wild type strains that were used to isolate the HSV and HCMV mutants. When tested against a number of 4-HQ's, 4-oxo-DHQ's and 4-oxo-DHTP's and other related classes of compounds all of the drugs were found to inhibit the wild-type virus with IC50 values ranging from less than 0.1-30 micro M. When these drugs were tested against the resistant viruses they were found to have IC50 values 5-10 fold higher then the parent virus.

USE - (M) is useful for selecting compounds that inhibit herpes viruses. (III) is useful for manufacture of medicinals for selectively treating diseases caused by herpes viruses such as herpes viral infection, or for selectively inhibiting herpes viruses, in a human host by administering a compound to a human in need of such treatment, where (III) inhibits herpes viruses by interaction with the binding domain in the viral DNA polymerase, and IC50 of (III) that inhibits a binding domain mutant herpes virus is at least 3 times, preferably 5 times greater than IC50 of the compound that inhibits the wild-type herpes virus which is the same strain as the mutant herpes virus (all claimed).

ABSTRACTED-PUB-NO:

WO 200206513A
EQUIVALENT-ABSTRACTS:

NOVELTY - Selecting (M) compounds that inhibit herpes viruses involves measuring IC50 of compound of interest (CI) that inhibits wild-type herpes virus (I) and domain mutant herpes virus (II) which is the same strain as (I), comparing IC50 of CI inhibiting (I) with IC50 of CI inhibiting (II) and selecting CI, where IC50 of CI that inhibits (II) is at least 3 times greater than IC50 of CI that inhibits (I).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a compound (III) for inhibiting herpes virus DNA polymerases, where passage of a wild type herpes virus in the presence of the compound results in a change of wild type herpes simplex virus type 1 (HSV-1) polymerases at amino acid 823 from valine to alanine, or of human cytomegalovirus (HCMV) polymerases at amino acid 823 from valine to alanine and at amino acid 824 from valine to leucine;

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(3) a mutant herpes virus polymerase amino acid molecule (V) having a sequence comprising 1238, 1240, 1235, or 1242 amino acids fully defined in the specification.

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MECHANISM OF ACTION - Inhibitor of herpes virus (claimed).

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ABSTRACTED-PUB-NO: US20020076789A
EQUIVALENT-ABSTRACTS: NOVELTY - Selecting (M) compounds that inhibit herpes viruses involves measuring IC50 of compound of interest (CI) that inhibits wild-type herpes virus (I) and domain mutant herpes virus (II) which is the same strain as (I), comparing IC50 of CI inhibiting (I) with IC50 of CI inhibiting (II) and selecting CI, where IC50 of CI that inhibits (II) is at least 3 times greater than IC50 of CI that inhibits (I). DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) a compound (III) for inhibiting herpes virus DNA polymerases, where passage of a wild type herpes virus in the presence of the compound results in a change of wild type herpes simplex virus type 1 (HSV-1) polymerases at amino acid 823 from valine to alanine, or of human cytomegalovirus (HCMV) polymerases at amino acid 823 from valine to alanine and at amino acid 824 from valine to leucine; (2) a mutant herpes virus DNA molecule (IV) having a nucleotide sequence comprising 3717, 3723, 3708, or 3729 base pairs fully defined in the specification; and (3) a mutant herpes virus polymerase amino acid molecule (V) having a sequence comprising 1238, 1240, 1235, or 1242 amino acids fully defined in the specification. ACTIVITY - Antiviral. MECHANISM OF ACTION - Inhibitor of herpes virus (claimed). Antiviral activity of nucleoside and non-nucleoside polymerase inhibitors against 4-oxo-dihydroquinoline (4-oxo-DHQ) resistant mutants was tested: In order to determine if the 4-hydroxyquinoline (4-HQ) binding domain mutations altered the sensitivity of the herpes simplex virus type-1 (HSV-1), HSV-2 and human cytomegalovirus (HCMV) mutants to both non-nucleoside (4-oxo-DHQ's) and nucleoside inhibitors (e.g., Acyclovir and ganciclovir) several of the mutants were tested in plaque reduction

assays against a series of non-nucleoside compounds including Foscarnet (PFA), 4-HQ's 4-oxo-DHQ's and 4-oxo-dihydrothienopyridine (4-oxo-DHTP). The mutants were also tested against series of nucleoside inhibitors including Acyclovir and ganciclovir. The activity of these compounds against the mutant was compared to their activity against the wild type strains that were used to isolate the HSV and HCMV mutants. When tested against a number of 4-HQ's, 4-oxo-DHQ's and 4-oxo-DHTP's and other related classes of compounds all of the drugs were found to inhibit the wild-type virus with IC50 values ranging from less than 0.1-30 micro M. When these drugs were tested against the resistant viruses they were found to have IC50 values 5-10 fold higher then the parent virus. USE - (M) is useful for selecting compounds that inhibit herpes viruses. (III) is useful for manufacture of medicinals for selectively treating diseases caused by herpes viruses such as herpes viral infection, or for selectively inhibiting herpes viruses, in a human host by administering a compound to a human in need of such treatment, where (III) inhibits herpes viruses by interaction with the binding domain in the viral DNA polymerase, and IC50 of (III) that inhibits a binding domain mutant herpes virus is at least 3 times, preferably 5 times greater than IC50 of the compound that inhibits the wild-type herpes virus which is the same strain as the mutant herpes virus (all claimed). WO 200206513A

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☐ 1. Document ID: US 6541009 B1

L7: Entry 1 of 5 File: USPT Apr 1, 2003

US-PAT-NO: 6541009
DOCUMENT-IDENTIFIER: US 6541009 B1
** See image for Certificate of Correction **

TITLE: Viral vaccines

DATE-ISSUED: April 1, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Inglis; Stephen Charles	Linton			GB
Boursnell; Michael Edward Griffith	Cambridge			GB
Minson; Anthony Charles	Great Shelford			GB

US-CL-CURRENT: 424/199.1; 424/205.1, 424/229.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 2. Document ID: US 6319703 B1

L7: Entry 2 of 5 File: USPT Nov 20, 2001

US-PAT-NO: 6319703
DOCUMENT-IDENTIFIER: US 6319703 B1

TITLE: Recombinant virus vectors

DATE-ISSUED: November 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Speck; Peter G.	Chicago	IL	60611	

US-CL-CURRENT: 435/235.1; 424/199.1, 424/205.1, 424/229.1, 424/231.1, 424/93.2, 435/236

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 3. Document ID: US 6287557 B1

L7: Entry 3 of 5 File: USPT Sep 11, 2001

US-PAT-NO: 6287557
DOCUMENT-IDENTIFIER: US 6287557 B1
** See image for Certificate of Correction **

TITLE: Methods of gene therapy using herpes viral vectors expressing GM-CSF

DATE-ISSUED: September 11, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Boursnell; Michael E. G.	Cambridge			GB
Inglis; Stephen C.	Cambridge			GB

US-CL-CURRENT: 424/93.2; 435/320.1, 435/455, 435/91.4, 435/91.41, 435/91.42

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 4. Document ID: US 5837261 A

L7: Entry 4 of 5 File: USPT Nov 17, 1998

US-PAT-NO: 5837261
DOCUMENT-IDENTIFIER: US 5837261 A
** See image for Certificate of Correction **

TITLE: Viral vaccines

DATE-ISSUED: November 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Inglis; Stephen Charles	Linton			GB
Boursnell; Michael Edward Griffith	Cambridge			GB
Minson; Anthony Charles	Great Shelford			GB

US-CL-CURRENT: 424/229.1; 424/231.1, 435/235.1, 435/236

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 5. Document ID: US 5665362 A

L7: Entry 5 of 5 File: USPT Sep 9, 1997

US-PAT-NO: 5665362
DOCUMENT-IDENTIFIER: US 5665362 A
** See image for Certificate of Correction **

TITLE: Viral vaccines

DATE-ISSUED: September 9, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Inglis; Stephen Charles	Cambridge			GB
Boursnell; Michael Edward Griffith	Cambridge			GB
Minson; Anthony Charles	Cambridge			GB

US-CL-CURRENT: 424/205.1; 424/229.1, 424/231.1

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END OF SEARCH HISTORY

All: 1018 Review: 82

Items 1 - 20 of 1018 Page 1 of 51 Next

1: Thomsen DR, Oien NL, Hopkins TA, Knechtel ML, Brideau RJ, Wathen MW, Homa FL. Related Articles, Links

Amino acid changes within conserved region III of the herpes simplex virus and human cytomegalovirus DNA polymerases confer resistance to 4-oxo-dihydroquinolines, a novel class of herpesvirus antiviral agents.
J Virol. 2003 Feb;77(3):1868-76.
PMID: 12525621 [PubMed - indexed for MEDLINE]

2: Brideau RJ, Knechtel ML, Huang A, Vaillancourt VA, Vera EE, Oien NL, Hopkins TA, Wieber JL, Wilkinson KF, Rush BD, Schwende FJ, Wathen MW. Related Articles, Links

Broad-spectrum antiviral activity of PNU-183792, a 4-oxo-dihydroquinoline, against human and animal herpesviruses.
Antiviral Res. 2002 Apr;54(1):19-28.
PMID: 11888654 [PubMed - indexed for MEDLINE]

3: Oien NL, Brideau RJ, Hopkins TA, Wieber JL, Knechtel ML, Shelly JA, Anstadt RA, Wells PA, Poorman RA, Huang A, Vaillancourt VA, Clayton TL, Tucker JA, Wathen MW. Related Articles, Links

Broad-spectrum antiherpes activities of 4-hydroxyquinoline carboxamides, a novel class of herpesvirus polymerase inhibitors.
Antimicrob Agents Chemother. 2002 Mar;46(3):724-30.
PMID: 11850254 [PubMed - indexed for MEDLINE]

4: Saijo M, Suzutani T, Morikawa S, Kurane I. Related Articles, Links

Genotypic characterization of the DNA polymerase and sensitivity to antiviral compounds of foscarnet-resistant herpes simplex virus type 1 (HSV-1) derived from a foscarnet-sensitive HSV-1 strain.
Antimicrob Agents Chemother. 2005 Feb;49(2):606-11.
PMID: 15673740 [PubMed - indexed for MEDLINE]

5: Williams SL, Hartline CB, Kushner NL, Harden EA, Bidanset DJ, Drach JC, Townsend LB, Underwood MR, Biron KK, Kern ER. Related Articles, Links

In vitro activities of benzimidazole D- and L-ribonucleosides against herpesviruses.
Antimicrob Agents Chemother. 2003 Jul;47(7):2186-92.
PMID: 12821466 [PubMed - indexed for MEDLINE]

6: Kushner NL, Williams SL, Hartline CB, Harden EA, Bidanset DJ, Chen X, Zemlicka J, Kern ER. Related Articles, Links

Efficacy of methylenecyclopropane analogs of nucleosides against herpesvirus replication in vitro.

Nucleosides Nucleotides Nucleic Acids. 2003 Dec;22(12):2105-19.
PMID: 14714760 [PubMed - indexed for MEDLINE]

☐ 7: Hwang YT, Zuccola HJ, Lu Q, Hwang CB. Related Articles, Links

A point mutation within conserved region VI of herpes simplex virus type 1 DNA polymerase confers altered drug sensitivity and enhances replication fidelity.
J Virol. 2004 Jan;78(2):650-7.
PMID: 14694096 [PubMed - indexed for MEDLINE]

☐ 8: Bestman-Smith J, Boivin G. Related Articles, Links

Drug resistance patterns of recombinant herpes simplex virus DNA polymerase mutants generated with a set of overlapping cosmids and plasmids.
J Virol. 2003 Jul;77(14):7820-9.
PMID: 12829822 [PubMed - indexed for MEDLINE]

☐ 9: Spector FC, Liang L, Giordano H, Sivaraja M, Peterson MG. Related Articles, Links

Inhibition of herpes simplex virus replication by a 2-amino thiazole via interactions with the helicase component of the UL5-UL8-UL52 complex.
J Virol. 1998 Sep;72(9):6979-87.
PMID: 9696789 [PubMed - indexed for MEDLINE]

☐ 10: Kamiyama T, Kurokawa M, Shiraki K. Related Articles, Links

Characterization of the DNA polymerase gene of varicella-zoster viruses resistant to acyclovir.
J Gen Virol. 2001 Nov;82(Pt 11):2761-5.
PMID: 11602787 [PubMed - indexed for MEDLINE]

☐ 11: Hwang YT, Smith JF, Gao L, Hwang CB. Related Articles, Links

Mutations in the Exo III motif of the herpes simplex virus DNA polymerase gene can confer altered drug sensitivities.
Virology. 1998 Jul 5;246(2):298-305.
PMID: 9657948 [PubMed - indexed for MEDLINE]

☐ 12: Marcelletti JF. Related Articles, Links

Synergistic inhibition of herpesvirus replication by docosanol and antiviral nucleoside analogs.
Antiviral Res. 2002 Nov;56(2):153-66.
PMID: 12367721 [PubMed - indexed for MEDLINE]

☐ 13: Michel D, Mertens T. Related Articles, Links

The UL97 protein kinase of human cytomegalovirus and homologues in other herpesviruses: impact on virus and host.
Biochim Biophys Acta. 2004 Mar 11;1697(1-2):169-80. Review.
PMID: 15023359 [PubMed - indexed for MEDLINE]

☐ 14: Knopf KW, Kaufman ER, Crumpacker C. Related Articles, Links

Physical mapping of drug resistance mutations defines an active center of the herpes simplex virus DNA polymerase enzyme.
J Virol. 1981 Sep;39(3):746-57.
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☐ 15: Tenney DJ, Yamanaka G, Voss SM, Cianci CW, Tuomari AV, Related Articles, Links

Sheaffer AK, Alam M, Colonno RJ.

Lobucavir is phosphorylated in human cytomegalovirus-infected and -uninfected cells and inhibits the viral DNA polymerase.
Antimicrob Agents Chemother. 1997 Dec;41(12):2680-5.
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16: Ono N, Iwayama S, Suzuki K, Sekiyama T, Nakazawa H, Tsuji T, Okunishi M, Daikoku T, Nishiyama Y. Related Articles, Links

Mode of action of (1'S,2'R)-9-[[1',2'-bis(hydroxymethyl) cycloprop-1'-yl] methyl]guanine (A-5021) against herpes simplex virus type 1 and type 2 and varicella-zoster virus.
Antimicrob Agents Chemother. 1998 Aug;42(8):2095-102.
PMID: 9687413 [PubMed - indexed for MEDLINE]

17: Andrei G, Fiten P, De Clercq E, Snoeck R, Opdenakker G. Related Articles, Links

Evaluating phenotype and genotype of drug-resistant strains in herpesviruses.
Mol Biotechnol. 2001 Jun;18(2):155-67.
PMID: 11471457 [PubMed - indexed for MEDLINE]

18: Bonneau AM, Kibler P, White P, Bousquet C, Dansereau N, Cordingley MG Related Articles, Links

Resistance of herpes simplex virus type 1 to peptidomimetic ribonucleotide reductase inhibitors: selection and characterization of mutant isolates.
J Virol. 1996 Feb;70(2):787-93.
PMID: 8551616 [PubMed - indexed for MEDLINE]

19: Terry BJ, Mazina KE, Tuomari AV, Haffey ML, Hagen M, Feldman A, Slusarchyk WA, Young MG, Zahler R, Field AK. Related Articles, Links

Broad-spectrum antiviral activity of the acyclic guanosine phosphonate (R,S)-HPMPG.
Antiviral Res. 1988 Dec 1;10(4-5):235-51.
PMID: 2852486 [PubMed - indexed for MEDLINE]

20: Lowe DM, Alderton WK, Ellis MR, Parmar V, Miller WH, Roberts GB, Fyfe JA, Gaillard R, Ertl P, Snowden W, et al Related Articles, Links

Mode of action of (R)-9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine against herpesviruses.
Antimicrob Agents Chemother. 1995 Aug;39(8):1802-8.
PMID: 7486922 [PubMed - indexed for MEDLINE]

Items 1 - 20 of 1018 Page 1 of 51 Next

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